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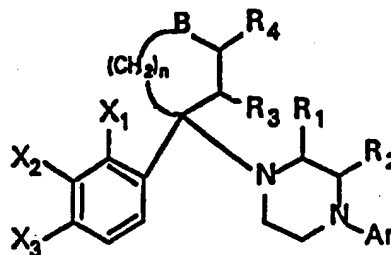
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>6</sup> : <b>C07D 295/18, 491/10, 211/86, 211/84, A61K 31/495</b></p>	<p><b>A1</b></p>	<p>(11) International Publication Number: <b>WO 98/03493</b> (43) International Publication Date: 29 January 1998 (29.01.98)</p>
<p>(21) International Application Number: PCT/US97/12616 (22) International Filing Date: 18 July 1997 (18.07.97) (30) Priority Data: 60/022,329 23 July 1996 (23.07.96) US (71) Applicant: NEUROGEN CORPORATION [US/US]; 35 N.E. Industrial Road, Bradford, CT 06405 (US). (72) Inventors: BLUM, Charles, A.; 100 Mirror Lane, Guilford, CT 06443 (US). HUTCHISON, Alan; 175 Bartlett Drive, Madison, CT 06443 (US). PETERSON, John, M.; 193 Lawrence Street, New Haven, CT 06511 (US). (74) Agents: RICHARDS, John; Ladas &amp; Parry, 26 West 61st Street, New York, NY 10023 (US) et al.</p>		<p>(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>

(54) Title: CERTAIN SUBSTITUTED BENZYLAMINE DERIVATIVES; A NEW CLASS OF NEUROPEPTIDE-Y1 SPECIFIC LIGANDS

(57) Abstract

This invention encompasses compounds of formula (I) and the pharmaceutically acceptable salts thereof, wherein X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> represent organic or inorganic substituents, n is 1, 2, or 3, R<sub>1</sub>-R<sub>4</sub> are hydrogen or organic substituents, and B is nitrogen, carbon, sulfur or oxygen, useful in the diagnosis and treatment of feeding disorders such as obesity and bulimia and cardiovascular diseases such as essential hypertension and congestive heart failure due to the binding of these compounds to human Neuropeptide Y1 receptors.



(I)

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CERTAIN SUBSTITUTED BENZYLAMINE DERIVATIVES:  
A NEW CLASS OF NEUROPEPTIDE-Y1 SPECIFIC LIGANDS

BACKGROUND OF THE INVENTION

Field of the Invention

5                   This invention relates to certain substituted benzylamine derivatives which selectively bind to mammalian Neuropeptide Y1 (NPY1) receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds and compositions in treating physiological disorders associated with an excess of Neuropeptide Y, especially feeding disorders and  
10   certain cardiovascular diseases.

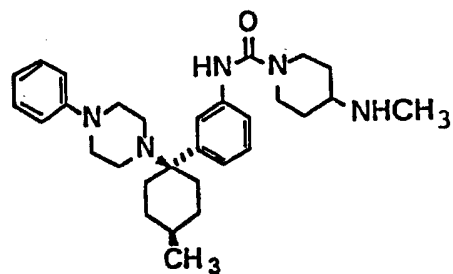
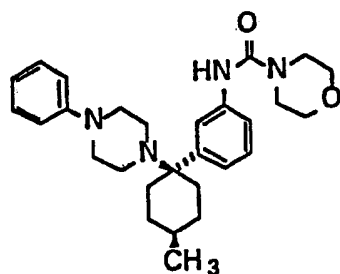
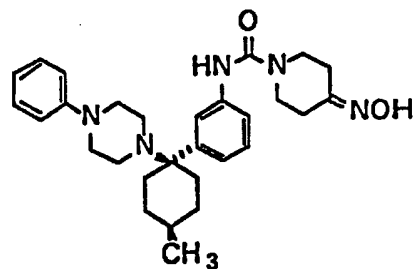
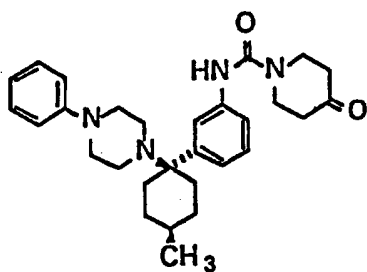
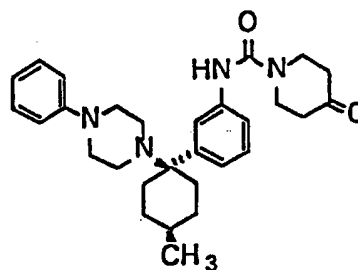
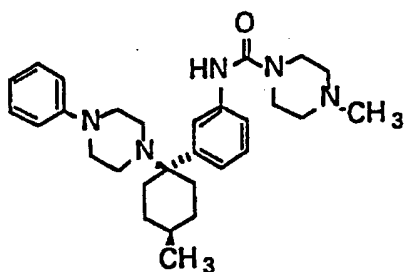
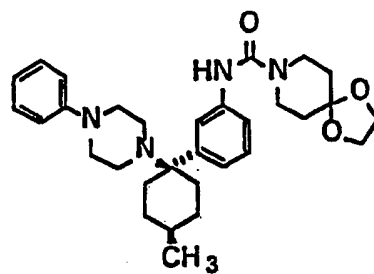
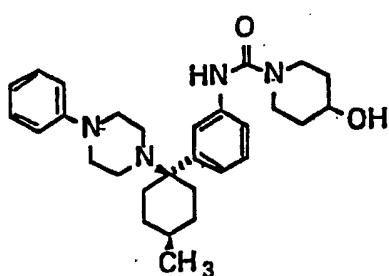
Description of the Related Art

                  Neuropeptide Y, a peptide first isolated in 1982, is widely distributed in the central and peripheral neurons and is responsible for a multitude of biological effects in the brain and the periphery. Various animal studies have shown that  
15   activation of Neuropeptide Y1 receptors is related to vasoconstriction, Wahlestedt et al., Regul. Peptides, 13: 307-318 (1986), McCauley and Westfall, J. Pharmacol. Exp. Ther. 261: 863-868 (1992), and Grundemar et al., Br. J. Pharmacol. 105: 45-50 (1992); and to stimulation of consummatory behavior, Flood and Morley, Peptides, 10: 963-966 (1989), Leibowitz and Alexander, Peptides, 12: 1251-1260 (1991), and Stanley et al.,  
20   Peptides, 13: 581-587 (1992).

                  Grundemar and Hakanson, TiPS, May 1994 [Vol. 15], 153-159, state that, in animals, Neuropeptide Y is a powerful stimuli of food intake, and an inducer of vasoconstriction leading to hypertension. They further point out that low levels of Neuropeptide Y is associated with loss of appetite. These reports clearly indicate that  
25   compounds that inhibit the activity of this protein will reduce hypertension and appetite in animals.

BRIEF DESCRIPTION OF THE DRAWING

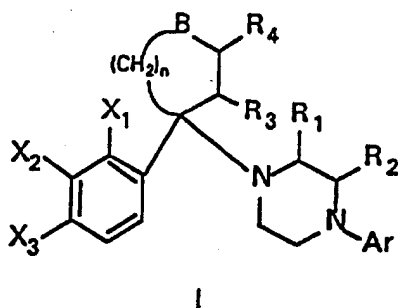
Figure 1 shows representative substituted benzylamines of the present invention.



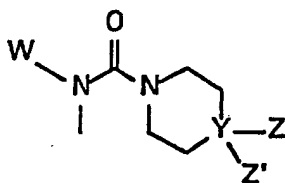
SUMMARY OF THE INVENTION

Compounds that interact with NPY1 receptors and inhibit the activity of Neuropeptide Y at those receptors are useful in treating physiological disorders associated with an excess of Neuropeptide Y, especially eating disorders such as, for example, obesity and bulimia, and certain cardiovascular diseases, such as, for example, hypertension. This invention provides novel compounds of Formula I which selectively bind to Neuropeptide Y1 (NPY1) receptors.

The novel compounds encompassed by the instant invention can be described by general Formula I:



wherein one of  $X_1$ ,  $X_2$ , and  $X_3$  is:



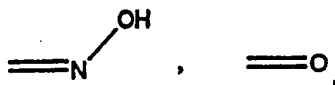
and the remaining members of the group of  $X_1$ ,  $X_2$ , and  $X_3$  are hydrogen; and

W is H or straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is Carbon, Nitrogen, Oxygen or Sulfur; and

when Y is carbon:

$Z = Z' = H$ ; or  $Z' = H$  and Z is:



hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, amino, mono or disubstituted straight or branched chain lower alkylamino; or

Z and Z' together may represent  $-O-(CH_2)_m-O-$  where  $m=2$  or  $3$ ;

when Y is nitrogen:

5           Z = Z' = H; or Z' = H; and Z is straight or a branched chain lower alkyl having 1-6 carbon atoms.

Ar is an aryl group preferably selected from the group consisting of phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain  
10 lower alkyl having 1-6 carbon atoms;

B is sulfur, oxygen,  $N(R_5)$  or  $C(R_5)(R_6)$ ;

n is 1, 2, or 3;

$R_1$  and  $R_2$  are the same or different and represent hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

15            $R_3$  and  $R_4$  are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

$R_5$  represents straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, or phenyl, 2-, 3-, or 4-pyridyl straight or branched  
20 chain lower alkyl having 1-6 carbon atoms; and

$R_6$  represents hydrogen, hydroxyl, amino, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, phenoxy, 2-, 3-, or 4-pyridyloxy, or  
- $(CH_2)_r-A'-(CH_2)_q-B'$  where

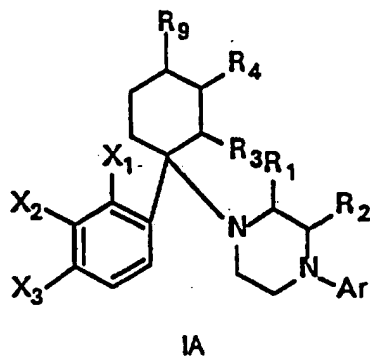
25           r is 0-5, q is 1-5, and A' is a direct bond, oxygen or sulfur, and

B' is hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or a branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, phenoxy, 2-, 3-, or 4-pyridyloxy, carboxyl, carboalkoxy, carboxamido, mono or dialkylcarboxamido, amino, or mono or dialkylamino.

30           Preferred compounds according to Formula I are those where Ar is optionally substituted phenyl, pyrimidinyl or pyridyl, B is carbon optionally substituted with phenyl or alkyl, and  $R_1-R_4$  are hydrogen. Particularly, preferred compounds or

Formula I are those where Ar is phenyl, pyrimidinyl or pyridyl, B is carbon optionally substituted with phenyl or alkyl, and R<sub>1</sub>-R<sub>4</sub> are hydrogen.

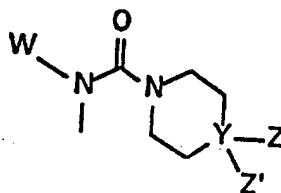
The invention also relates to compounds of Formula IA:



where

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

wherein one of X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> and is:



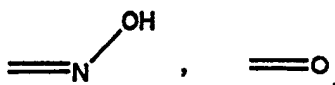
and the remaining members of the group of X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> are hydrogen; and

W is H or straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is Carbon, Nitrogen, Oxygen or Sulfur;

when Y is carbon:

Z = Z' = H; or Z' = H and Z is:



hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, amino, mono or disubstituted straight or branched chain lower alkylamino; or

Z and Z' together may represent  $-O-(CH_2)_m-O-$  where  $m=2$  or  $3$ ;

when Y is nitrogen:

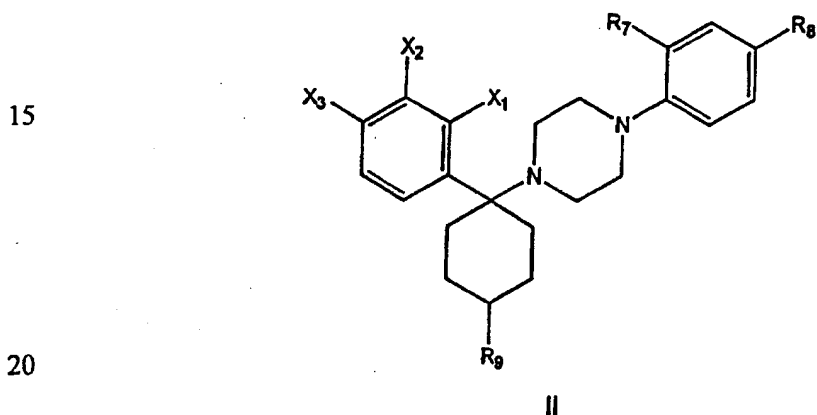
Z is hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms; and Z' is nothing.

5  $R_1$  and  $R_2$  are the same or different and represent hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

$R_3$  and  $R_4$  are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; and

10  $R_5$  represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl.

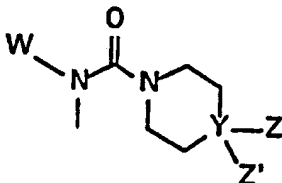
The invention further encompasses compounds of Formula II:



where  $R_7$  and  $R_8$  are different and represent hydrogen or Fluorine;

$R_9$  represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl;

25 wherein one of  $X_1$ ,  $X_2$ , and  $X_3$  is:



30 and the remaining members of the group of  $X_1$ ,  $X_2$ , and  $X_3$  are hydrogen; and

W is H or straight or branched chain lower alkyl having 1-6 carbon atoms;



Y is Carbon, Nitrogen, Oxygen or Sulfur;

when Y is carbon:

Z = Z' = H; or Z' = H and Z is:



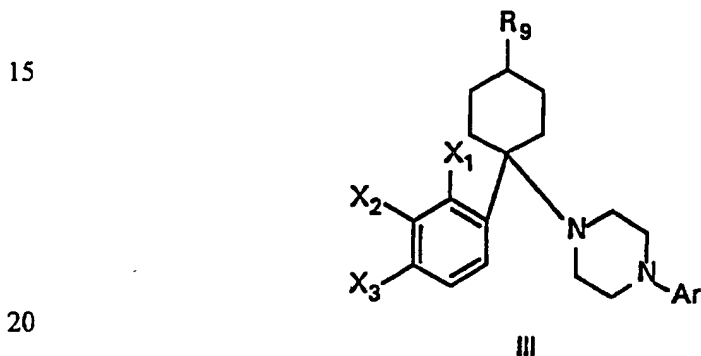
hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, amino, mono or disubstituted straight or branched chain lower alkylamino; or

Z and Z' together may represent  $-\text{O}-(\text{CH}_2)_m-\text{O}-$  where  $m=2$  or  $3$ ; and

10 when Y is nitrogen:

Z is hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms and Z' is nothing.

The invention also relates to compounds of Formula III:



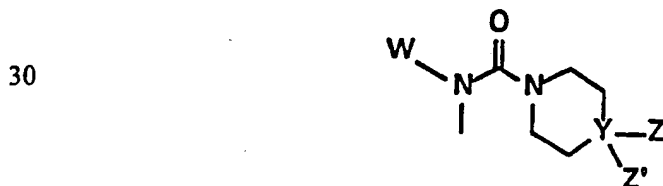
where

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

25

R<sub>9</sub> represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenyl;

wherein one of X<sub>1</sub>, X<sub>2</sub>, and X<sub>3</sub> is:



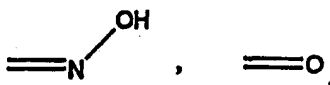
and the remaining members of the group of  $X_1$ ,  $X_2$ , and  $X_3$  are hydrogen; and

W is H or straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is Carbon, Nitrogen, Oxygen or Sulfur;

5 when Y is carbon:

$Z = Z' = H$ ; or  $Z' = H$  and Z is:



10 hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, amino, mono or disubstituted straight or branched chain lower alkylamino; or

Z and Z' together may represent  $-O-(CH_2)_m-O-$  where  $m = 2$  or  $3$ ;

when Y is nitrogen:

15 Z is hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms;

Representative compounds of the present invention, which are encompassed by Formula I-III, include, but are not limited to the compounds in Figure 1 and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, 20 sulfuric, sulfinic, formic, toluene sulfonic, hydroiodic, acetic and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of Formula I-III. Those skilled in the art will recognize various synthetic 25 methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I-III.

The invention encompasses both diastereomers of the compounds having 1,4-substitution on the cyclohexane ring, i.e., the invention encompasses both 30 cis-, and trans-1,4-cyclohexanes. Preferred compounds of the invention having 1,4-substitution on the cyclohexane ring are those where the nitrogen atom forming the piperazine ring and the alkyl or phenyl group in the 4-position of the cyclohexane ring

are "cis" with respect to each other. Thus, preferred compounds of the invention having such substitution are those that are cis-1-piperazinyl-4-alkyl or phenyl-cyclohexanes.

#### DETAILED DESCRIPTION OF THE INVENTION

5 By "aryl" and "Ar" is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which can optionally be unsubstituted or substituted with e.g., halogen, lower alkyl, lower alkoxy, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, 10 heteroaryl, and hydroxy.

By "alkyl" and "lower alkyl" is meant straight and branched chain alkyl groups having from 1-6 carbon atoms.

By "lower alkoxy" and "alkoxy" is meant straight and branched chain alkoxy groups having from 1-6 carbon atoms.

15 By "halogen" is meant fluorine, chlorine, bromine and iodine.

The pharmaceutical utility of compounds of this invention is indicated by the following assay for human NPY1 receptor activity.

As the compounds of Formula I are effective Neuropeptide Y1 receptor antagonists, these compounds are of value in the treatment of a wide variety of clinical 20 conditions which are characterized by the presence of an excess of Neuropeptide Y. Thus, the invention provides methods for the treatment or prevention of a physiological disorder associated with an excess of Neuropeptide Y, which method comprises administering to a mammal in need of said treatment an effective amount of a compound of Formula I or a pharmaceutically acceptable salt, solvate or prodrug 25 thereof. The term "physiological disorder associated with an excess of Neuropeptide Y" encompasses those disorders associated with an inappropriate stimulation of Neuropeptide Y receptors, regardless of the actual amount of neuropeptide Y present in the locale.

These physiological disorders may include: 30 disorders or diseases pertaining to the heart, blood vessels or the renal system, such as vasospasm, heart failure, shock, cardiac hypertrophy increased blood pressure, angina, myocardial infarction, sudden cardiac death, arrhythmia, peripheral

vascular disease, and abnormal renal conditions such as impaired flow of fluid, abnormal mass transport, or renal failure;

conditions related to increased sympathetic nerve activity for example, during or after coronary artery surgery, and operations and surgery in the

5 gastrointestinal tract;

cerebral diseases and diseases related to the central nervous system, such as cerebral infarction, neurodegeneration, epilepsy, stroke, and conditions related to stroke, cerebral vasospasm and hemorrhage, depression, anxiety schizophrenia, and dementia;

10 conditions related to pain or nociception;

diseases related to abnormal gastrointestinal motility and secretion, such as different forms of ileus, urinary incontinence, and Crohn's disease;

abnormal drink and food intake disorders, such as obesity, anorexia, bulimia, and metabolic disorders;

15 diseases related to sexual dysfunction and reproductive disorders;

conditions or disorders associated with inflammation;

respiratory diseases, such as asthma and conditions related to asthma and bronchoconstriction; and

diseases related to abnormal hormone release, such as leutinizing hormone, growth hormone, insulin, and prolactin. See U.S. Patent 5,504,094.

The pharmaceutical utility of compounds of this invention is indicated by the following assay for human NPY1 receptor activity.

#### Assay for Human NPY1 Receptor Binding Activity

##### Membrane Preparation:

25 Baculovirus-infected Sf9 cells expressing recombinant human NPY Y1 receptors were harvested at 42-48 hours at which time batches of 500 mL of cell suspension were pelleted by centrifugation. Each pellet was resuspended in 30 mL of lysis buffer (10 mM HEPES, 250 mM sucrose, 0.5 µg/ml leupeptin, 2 µg/ml Aprotinin, 200 µM PMSF and 2.5 mM EDTA, pH 7.4) and gently homogenized by 50  
30 strokes using a dounce homogenizer. The homogenate was centrifuged at 4°C. for 10 minutes at 536 x g to pellet the nuclei. The supernatant was collected into a fresh tube and centrifuged twice in the same buffer at 48,000 x g for 40 minutes. The final pellet

was resuspended in 10 mL of PBS containing 5 mM EDTA by dounce homogenization and stored in aliquots at -80°C.

[<sup>125</sup>I]PYY Binding Assay:

Purified membranes were washed by PBS and resuspended by gentle pipetting in binding buffer [50 mM Tris(HCl), 5 mM KCl, 120 mM NaCl, 2 mM CaCl<sub>2</sub>, 1 mM MgCl<sub>2</sub>, 0.1% bovine serum albumin (BSA), pH 7.4]. Membranes (5μg) were added to siliconized (Sigmacote, Sigma) polypropylene tubes in addition to 0.050 nM [<sup>125</sup>I] PYY for (porcine) for competition analysis or 0.010-0500 nM [<sup>125</sup>I] PYY (porcine) for saturation analysis. For evaluation of guanine nucleotide effects on receptor affinity, GTP was added at a final concentration of 100 μM. Cold displacers were added at concentrations ranging from 10<sup>-12</sup> M to 10<sup>-6</sup> M to yield a final volume of 0.250 mL. Nonspecific binding was determined in the presence of 1 μM NPY(human) and accounted for less than 10% of total binding. Following a 2 hour incubation at room temperature, the reaction was terminated by rapid vacuum filtration. Samples were filtered over presoaked GF/C Whatman filters (1.0% polyethylenimine for 2 hours) and rinsed 2 times with 5 mLs cold binding buffer lacking BSA. Remaining bound radioactivity was measured by gamma counting. To estimate the Bmax, Kd and Ki, the results of binding experiments were analyzed using SigmaPlot software (Jandel).

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any

method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active  
5 ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating  
10 agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

15 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

20 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for  
25 example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene  
30 oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more

coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxides for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for

example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including  
5 synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at  
10 ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local  
15 anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

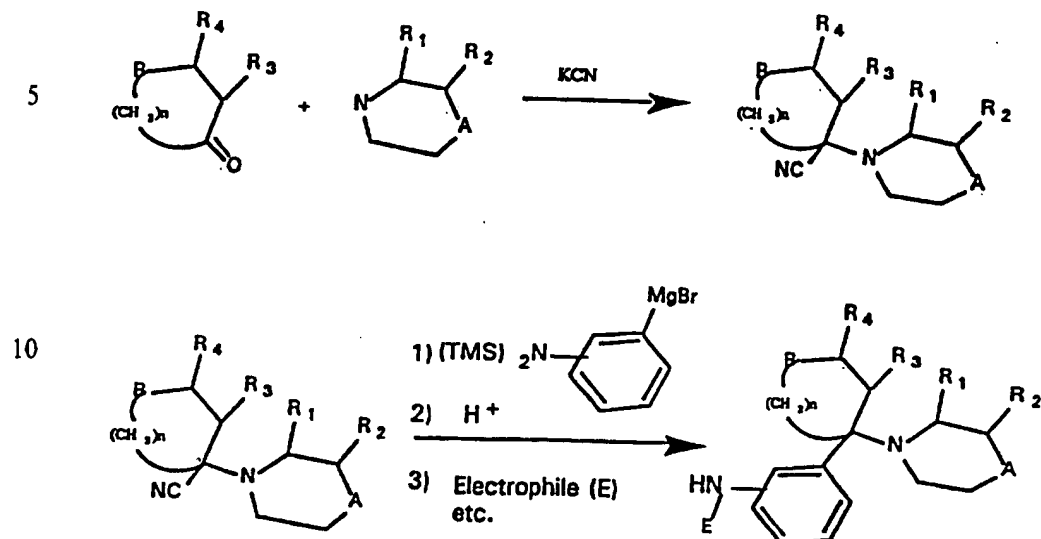
Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage  
20 form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the  
25 specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

An illustration of the preparation of compounds of the present invention is given in Scheme I. Those having skill in the art will recognize that the  
30 starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention.



Scheme 1



where

A is ArN or ArCH where Ar is phenyl, 2, 3, or 4-pyridyl, 2 or 3-thienyl, 2, 4 or 5-pyrimidyl either unsubstituted or mono or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

20 B is sulfur, oxygen NR<sub>5</sub> or CR<sub>5</sub>R<sub>6</sub>

n is 1, 2, or 3;

R<sub>1</sub> and R<sub>2</sub> are the same or different and represent hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

25 R<sub>3</sub> and R<sub>4</sub> are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms;

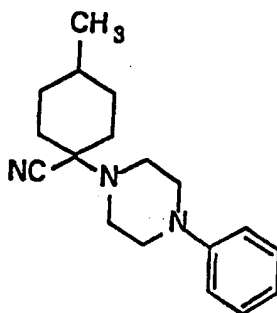
R<sub>5</sub> represents straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl, 2, 3, or 4-pyridyl, or phenyl, 2, 3, or 4-pyridyl straight or branched chain lower alkyl having 1-6 carbon atoms;

30 R<sub>6</sub> represents hydrogen, hydroxyl, amino, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2, 3, or 4-pyridyl, phenyloxy, 2, 3, or 4-pyridyloxy, or ]

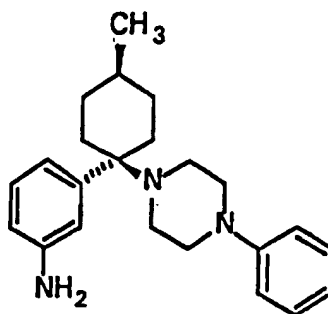
-(CH<sub>2</sub>)<sub>r</sub>-A'-(CH<sub>2</sub>)<sub>q</sub>-B' where r represents 0-5 and q represents 1-5 and A' is a direct bond, oxygen or sulfur and B' is hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms, phenyl, 2, 3, or 4-pyridyl, phenyloxy, 2, 3, or 4-pyridyloxy, carboxyl, carboalkoxy, unsubstituted, mono or dialkylcarboxamido, amino, or mono or dialkylamino.

The invention is illustrated further by the following examples which are not to be construed as limiting the invention in scope or spirit to the specific procedures and compounds described in them.

Example I



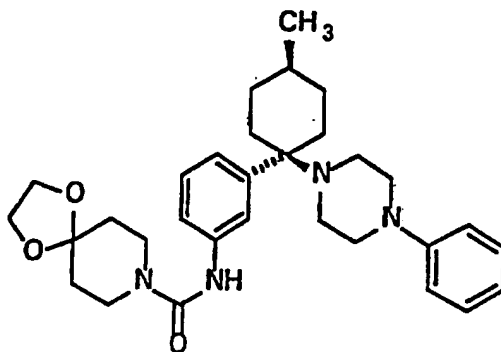
N-Phenylpiperazine (37 mL, 40 g, 245 mmol) was suspended in 300 mL water. The pH was adjusted to between 3 and 4 using 10% HCl. 4-Methyl cyclohexanone (30 mL, 27 g, 244 mmol) was added followed by KCN (16g, 245 mmol). The mixture was stirred 15 hours at room temperature during which time the product solidified. The product was collected by filtration, washed with water, then dried in the vacuum oven overnight at 50°C. to give 58 g (84% yield) desired product as a roughly 2 : 1 mixture of diastereomers. Tlc R<sub>f</sub> = 0.25 and 0.3 (9:1, Hexanes/Ethyl Acetate).

Example II

5

A 1 Molar THF solution of 3-[Bis(trimethylsilyl)amino]-  
phenylmagnesium chloride (100 mL, 0.1 mol) was added to a solution of 1-cyano-1-  
10 (4-phenylpiperazine-1-yl)-4-methylcyclohexane (10g, 0.035 mol) in dry THF (100 mL).  
The reaction mixture was heated to 65°C. for 2h, cooled to room temperature and  
quenched by dropwise addition of saturated NH<sub>4</sub>Cl solution. The magnesium salts were  
filtered, rinsed with THF and the filtrate was concentrated under reduced pressure. The  
15 residue was dissolved in EtOH (70 mL), 5% HCl solution (20 mL) was added, and the  
mixture stirred for 30 min. at room temperature. The mixture was filtered and the  
filtrate was concentrated under reduced pressure. The residue was suspended in H<sub>2</sub>O,  
made basic with 10 N NaOH and then extracted with EtOAc (3x). The combined  
extracts were washed with H<sub>2</sub>O (1x) and brine (1x), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and  
20 concentrated under reduced pressure. The residue was filtered through silica gel  
(1:4/ EtOAc:hexanes) and concentrated to give a pale yellow solid. Recrystallization  
from isopropyl alcohol yielded white needles of 1-(3-aminophenyl)-1-(4-  
phenylpiperazine-1-yl)-4-methyl-cyclohexane (cis isomer) in 38% yield.  
mp = 142-144°C.

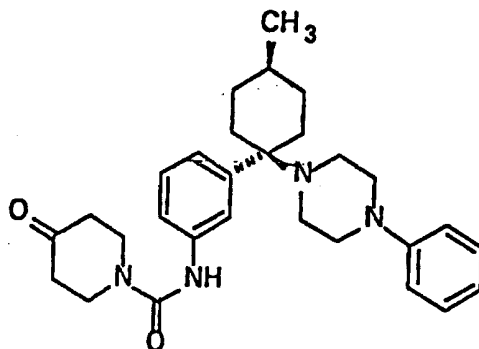
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Example III

30

A solution of 1-(3-aminophenyl)-1-(4-phenylpiperazin-1-yl)-4-methylcyclohexane (cis isomer, 246 mg, 0.705 mmol) and triethylamine (147  $\mu$ L, 1.06 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (15 mL) was brought to  $0^\circ\text{C}$ . using an ice bath. Phosgene (1.93 M in toluene, 438  $\mu$ L, 0.846 mmol) was added dropwise and the resulting mixture was stirred at  $0^\circ\text{C}$ ., under a dry  $\text{N}_2$  atmosphere, for 30 minutes. 1,4-dioxo-8-azaspiro[4.5]decane (181  $\mu$ L, 1.41 mmol) was added via syringe and the reaction was allowed to come to room temperature. After 2h the reaction mixture was diluted with an equal volume of  $\text{CH}_2\text{Cl}_2$ , washed with  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give an off-white solid. The solid was washed with 30% EtOAc/hexanes to give the free base of N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl]-1,4-dioxo-8-azaspiro[4.5]decane-8-carboxamide (cis isomer) as a white solid. mp =  $245\text{--}247^\circ\text{C}$ .

#### Example IV

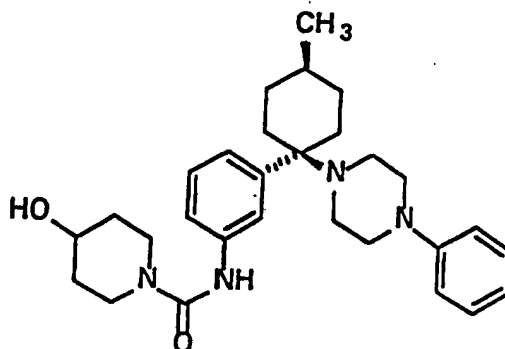


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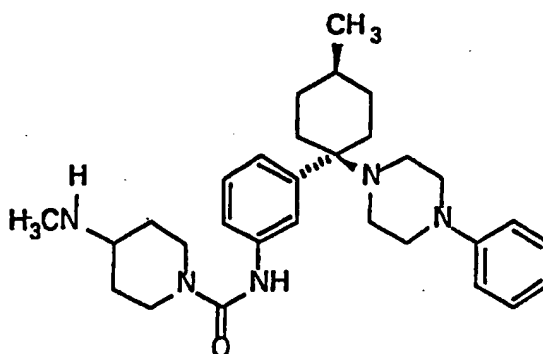
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A solution of N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl]-1,4-dioxo-8-azaspiro[4.5]decane-8-carboxamide (cis isomer) (34 mg, 0.066 mmol) was dissolved in 4 mL of 6N HCl and the clear homogeneous solution was allowed to stand for 1h at room temperature. The reaction mixture was made basic with 1N NaOH, extracted with  $\text{CH}_2\text{Cl}_2$ , dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to give the crude ketone. The residue was triturated with 30% EtOAc/hexanes to yield colorless crystals of 4-(oxo)-N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl]-1-piperidinecarboxamide (cis isomer). mp =  $\sim 173^\circ\text{C}$ . (decomp.).

25

Example V

A solution of 4-(oxo)-N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl]-1-piperidinecarboxamide (cis isomer) (34 mg, 0.072 mmol) in anhydrous EtOH was treated with excess NaBH<sub>4</sub> (14 mg, 0.36 mmol) and the resulting solution was stirred at room temperature for 1h. The reaction was quenched with excess saturated NH<sub>4</sub>Cl (aq.) then extracted with EtOAc (3x). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated under reduced pressure, and triturated with 30% EtOAc/hexanes to give 4-(hydroxy)-N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)-cyclohexyl]phenyl]-1-piperidinecarboxamide (cis isomer), as a white powder. The HCl salt was prepared by adding excess saturated EtOAc/HCl solution to the free base in dry MeOH. Concentration of the homogeneous solution yielded a white solid which was washed with EtOAc. mp = 144-145°C.

Example VI

Methylamine hydrochloride (37 mg, 0.546 mmol) was added to a solution of 4-(oxo)-N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl]-1-piperidinecarboxamide (cis isomer) (43 mg, 0.091 mmol) in THF/MeOH (1:1) and stirred at room temperature. When all the methylamine hydrochloride had dissolved, 5 NaCNBH<sub>4</sub> (6 mg, 0.091 mmol) was added and the reaction allowed to stir overnight at room temperature. The reaction mixture was concentrated, dissolved in an excess of 3N HCl, and the aqueous solution washed with ether (3x). The aqueous solution was made basic with 10N NaOH, extracted with EtOAc (4x), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give 4-(methylamino)-N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)-  
10 cyclohexyl]phenyl]-1-piperidinecarboxamide (cis isomer) as a clear oil. The HCl salt was prepared by adding excess saturated EtOAc/HCl solution to the free base in dry MeOH. Concentration of the homogeneous solution yielded a white solid which was washed with EtOAc. mp = 154-155°C.

#### Example VII

15 The following compounds were prepared essentially according to the procedure described in Example III:

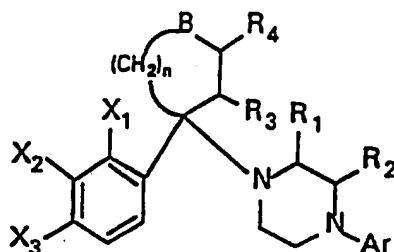
- a) N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl]-4-morpholinecarboxamide dihydrochloride (cis isomer: Compound 5). mp = 188-190°C.
- b) 4-methyl-N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)-cyclo-  
20 hexyl]phenyl]-1-piperazinecarboxamide trihydrochloride (cis isomer: Compound 6). mp = 143-145°C.
- c) 4-(hydroxyimino)-N-[3-[4-methyl-1-(4-phenyl-1-piperazinyl)-cyclohexyl]phenyl]-1-piperidinecarboxamide (cis isomer: Compound 7). mp = 193-195°C.

25 The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the  
30 present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

CLAIMS

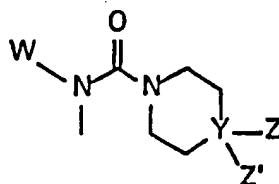
1. A compound of the formula:

5



wherein one of  $X_1$ ,  $X_2$  and  $X_3$  is

10



and the remaining members of the group of  $X_1$ ,  $X_2$ , and  $X_3$  are hydrogen;

15

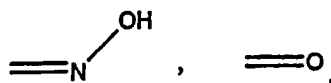
W is H or straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is Carbon, Nitrogen, Oxygen or Sulfur; wherein

when Y is carbon:

Z and Z' jointly form

20



$-O-(CH_2)_m-O-$  where  $m=2$  or  $3$ ;

or Z' is hydrogen and Z is hydrogen, hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, amino, mono or disubstituted straight or branched chain lower alkylamino; or

25

when Y is nitrogen:

and Z is hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms and Z' does not exist; and pharmaceutically acceptable salts thereof;

30

Ar is an aryl group selected from the group consisting of phenyl, 2-, 2-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl

having 1-6 carbon atoms;

B is sulfur, oxygen,  $N(R_5)$  or  $C(R_5)(R_6)$ ;

n is 1, 2, or 3;

$R_1$  and  $R_2$  are the same or different and represent hydrogen, or straight  
5 or branched chain lower alkyl having 1-6 carbon atoms;

$R_3$  and  $R_4$  are the same or different and represent hydrogen, straight or  
branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain  
lower alkoxy having 1-6 carbon atoms;

$R_5$  represents hydrogen straight or branched chain lower alkyl having  
10 1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, or phenyl, 2-, 3-, or 4-pyridyl straight or  
branched chain lower alkyl having 1-6 carbon atoms; and

$R_6$  represents hydrogen, hydroxyl, amino, straight or branched chain  
lower alkyl having 1-6 carbon atoms, straight or branched chain lower alkoxy having  
1-6 carbon atoms, phenyl, 2-, 3-, or 4-pyridyl, phenoxy, 2-, 3-, or 4-pyridyloxy, or  
15  $-(CH_2)_r-A^1-(CH_2)_q-B^1$  where

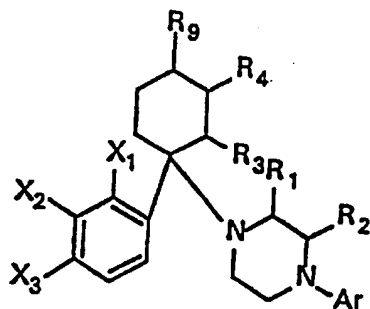
r is 0-5, q is 1-5, and  $A^1$  is a direct bond, oxygen or sulfur, and

$B^1$  is hydrogen, straight or branched chain lower alkyl having 1-6  
carbon atoms, straight or branched chain lower alkoxy having 1-6 carbon atoms,  
phenyl, 2-, 3-, or 4-pyridyl, phenoxy, 2-, 3-, or 4-pyridyloxy, carboxyl, carboalkoxy,  
20 carboxamido, mono or dialkylcarboxamido, amino, or mono or dialkylamino.

2. A compound as claimed in claim 1, wherein Ar is selected from phenyl,  
pyrimidinyl or pyridyl and is optionally substituted mono or disubstituted with halogen,  
hydroxy or straight or branched chain alkyl groups of 1-6 carbon atoms.

3. A compound as claimed in claim 1, where B is carbon optionally  
25 substituted with phenyl or alkyl.

4. A compound of formula:

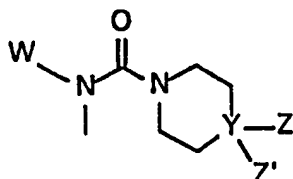




where

Ar is phenyl, 2-, 3-, or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

5 wherein one of  $X_1$ ,  $X_2$ , and  $X_3$  is:



10

and the remaining members of the group of  $X_1$ ,  $X_2$ , and  $X_3$  are hydrogen; and

W is H or straight or branched chain lower alkyl having 1-6 carbon atoms;

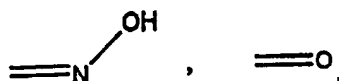
Y is Carbon, Nitrogen, Oxygen or Sulfur;

15

when Y is carbon:

Z and Z' together may represent  $-O-(CH_2)_m-$  where  $m=2$  or

3; or



20

or  $Z' = H$  and Z is hydrogen, hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, amino, mono or disubstituted straight or branched chain lower alkylamino; or

when Y is nitrogen:

25

Z is hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms and  $Z'$  is nothing;

$R_1$ , and  $R_2$  are the same or different and represent hydrogen, or straight or branched chain lower alkyl having 1-6 carbon atoms;

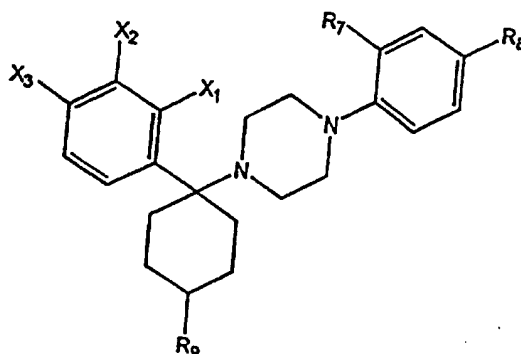
$R_3$  and  $R_4$  are the same or different and represent hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or straight or branched chain lower alkoxy having 1-6 carbon atoms; and

30

$R_5$  represents hydrogen, straight or branched chain lower alkyl having

1-6 carbon atoms, phenyl.

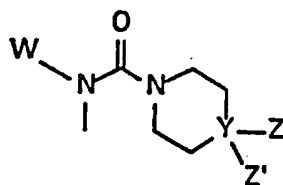
5. A compound of Formula II:



where  $R_7$  and  $R_8$  are different and represent hydrogen or Fluorine;

$R_9$  represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, phenyl;

wherein one of  $X_1$ ,  $X_2$  and  $X_3$  is:



and the remaining members of the group of  $X_1$ ,  $X_2$  and  $X_3$  are hydrogen; and

W is Carbon, Nitrogen, Oxygen or Sulfur;

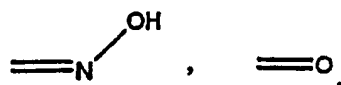
when Y is carbon:

$Z'$  is hydrogen and Z is hydrogen, hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, amino, mono or disubstituted straight or

branched chain lower alkylamino; or

Z and  $Z'$  together may represent  $-O-(CH_2)_m-O-$  where  $m=2$  or

3; or



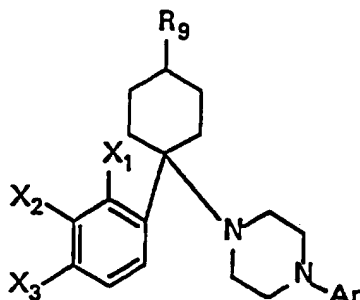
and

when Y is nitrogen:

Z is hydrogen or straight or branched chain lower alkyl having 1-6

carbon atoms and Z' is nothing.

6. A compound of Formula III

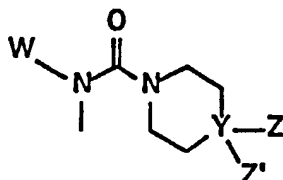


10 where

Ar is phenyl, 2-, 3- or 4-pyridyl, 2- or 3-thienyl, 2-, 4- or 5-pyrimidyl, each of which is optionally mono- or disubstituted with halogen, hydroxy, or straight or branched chain lower alkyl having 1-6 carbon atoms;

15 R<sub>9</sub> represents hydrogen, straight or branched chain lower alkyl having 1-6 carbon atoms, or phenyl;

wherein one of X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> is:



20

and the remaining members of the group of X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are hydrogen; and

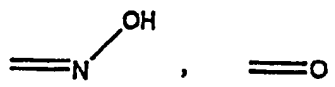
25 W is H or straight or branched chain lower alkyl having 1-6 carbon atoms;

Y is Carbon, Nitrogen, Oxygen or Sulfur;

when Y is carbon:

30 Z' is hydrogen and Z is hydrogen or hydroxy, straight or branched chain lower alkoxy having 1-6 carbon atoms, amino, mono or disubstituted straight or branched chain lower alkylamino; or

Z and Z' together may represent



or  $-O-(CH_2)_m-O-$  where  $m=2$  or  $3$ ;

when Y is nitrogen:

Z is hydrogen or straight or branched chain lower alkyl having 1-6 carbon atoms;

5 7. A compound as claimed in claim 1, wherein  $R_1$  and  $R_2$  are both hydrogen and Ar is phenyl.

8. A compound as claimed in claim 1, wherein  $n$  is 2,  $R_3$  and  $R_4$  are both hydrogen and B is  $C(R_5)(R_6)$  wherein  $R_5$  is lower alkyl and  $R_6$  is hydrogen.

9. A compound as claimed in claim 8, wherein  $R_5$  is methyl.

10 10. A compound as claimed in any of the preceding claims, wherein  $X_1$  and  $X_3$  are both hydrogen.

11. A compound as claimed in claim 10, wherein Y is  $C=O$ ,  $\text{>N-CH}_3$ ,  $\text{>C=NOH}$ ,  $\text{CHOH}$ ,  $\text{>C-NH-CH}_3$  or



12. A compound as claimed in claim 1, selected from the group consisting of N-{3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl}-1,4-dioxo-8-azaspiro[4,5]decane-8-carboxamide (cis isomer), 4-(oxo)-N-{3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl}-1 piperidinecarboxamide (cis isomer), 4-(methylamino)-N-{3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl}-1-piperidinecarboxamide (cis isomer), N-{3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl}-4-morpholonecarboxamide dihydrochloride (cis isomer), 4-methyl-N-{3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl}-1-piperazinecarboxamide trihydrochloride (cis isomer) and 4-(hydroxyimino)-N-{3-[4-methyl-1-(4-phenyl-1-piperazinyl)cyclohexyl]phenyl}-1-piperidinecarboxamide (is isomer).

13. A method of treating or preventing a physiological condition in a mammal characterized by the presence of an excess of Neuropeptide Y which comprises administering to a mammal in need of such treatment an effective amount of a compound as claimed in claim 1, 2, 3, 4, 5, 6 or 12.

14. A pharmaceutical composition comprising a compound as claimed in claim 1, 2, 3, 4, 5, 6, or 12 and pharmaceutically acceptable carrier.

15. A medicine comprising a compound as claimed in any of claims 1, 2, 3, 4, 5, 6 or 12.
16. Use of a compound as claimed in any of claims 1, 2, 3, 4, 5, 6 or 12 for preparation of a medicament for treating or preventing a physiological condition in a mammal characterized by excess Neuropeptide Y.
- 5

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 97/12616

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D295/18 C07D491/10 C07D211/86 C07D211/84 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 395 312 A (JOHN WYETH & BROTHER LIMITED) 31 October 1990 see the whole document ---	1-16
A	BULLETIN FAC, PHARMACY, vol. 31, no. 3, 1993, CAIRO, pages 475-479, XP000566787 ---	1-16
A	US 4 845 221 A (GARY P. STACK ET. AL) 4 July 1989 ---	1-16
P,A	WO 96 40660 A (PFIZER INC) 19 December 1996 see the whole document -----	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

5 November 1997

Date of mailing of the international search report

25. 11. 97

Name and mailing address of the ISA

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Authorized officer

Luyten, H

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 12616

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos. . . . .  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 13  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos. . . . .  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos. . . . .  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/12616

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